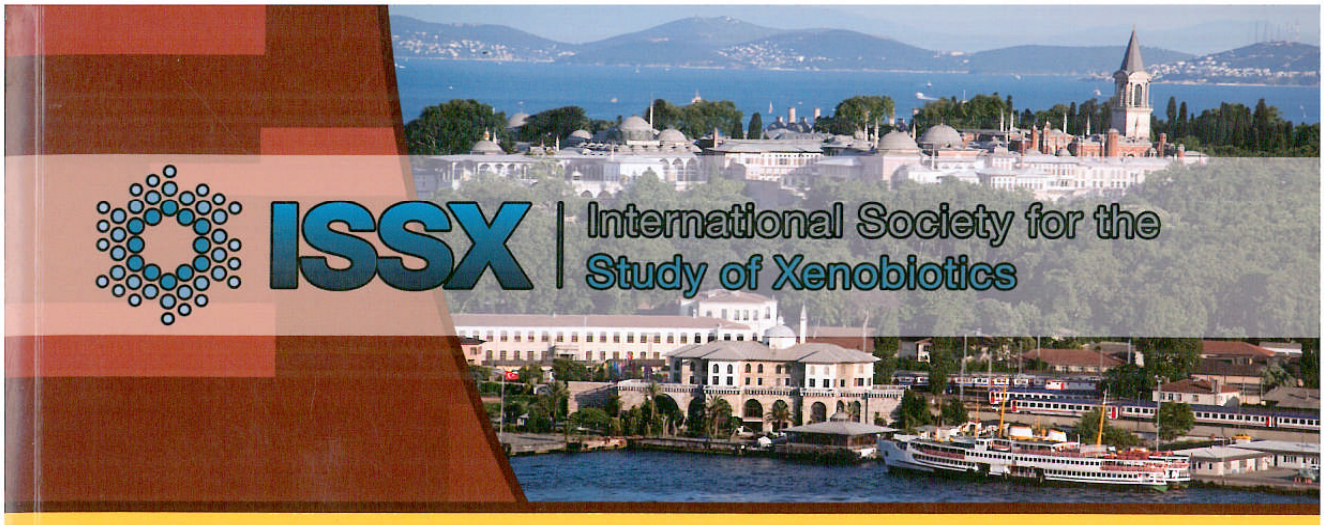

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PROGRAM & ABSTRACTS

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Changes in the enzymatic activities of myeloperoxidase (MPO), superoxide dismutase (SOD) and lactate dehydrogenase (LDH) as well as reduced glutathione (GSH), protein thiols (Pr-SHs) and nitric oxide (NO) contents of the brain were determined. In addition, brain content of thiobarbituric acid reactive substances (TBARS) was measured as an index of lipid peroxidation. Sub-chronic PQ administration resulted in 50% mortality and significant reductions in animals' weight gain as compared to the normal group. On the biochemical level, PQ provoked remarkable brain damage noted by elevation of neutrophils MPO activity accompanied by decreased activities of cytosolic SOD and LDH, depletion of GSH and Pr-SHs contents as well as increased production of NO and TBARS. Daily treatment with any of the chosen agents for 6 weeks significantly ameliorated the PQ-induced reduction in body weight gain of rats and protected against most of PQ-induced brain biochemical changes. It could be concluded that deprenyl, quercetin, green tea and malt extract offered remarkable neuroprotection against PQ-induced brain injury. The most pronounced neuroprotective effects was produced by deprenyl which was the only drug that completely prevented PQ-induced mortality.

P299. BENEFIT EFFECT OF NALOXONE IN BENZODIAZEPINES INTOXICATION: FINDINGS OF A PRELIMINARY STUDY

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Background: Naloxone, as a low-priced and available drug, may be useful in improvement of signs and symptoms of benzodiazepines intoxication. The aim of this study was assessment of its effect on benzodiazepines poisoning. Methods: In this clinical trial study, patients with typical signs and symptoms of benzodiazepines poisoning who referred to a poisoning center in Tehran in 2008 were selected. After recording of patient characteristics, supportive treatment initiated and patients randomly assigned to IV injection of two 0.4 mg naloxone ampules group (case) or control group. Their signs and symptoms were evaluated 0.5 hour later again. Each of diazepam, clonazepam and alperazolam drug group had 30 patients and lorazepam drug group had 26 patients which half of the patients in each drug group received naloxone. Results: Most of participants were female and the mean age was 28 yr. There were no significant differences between case and control groups in age, sex, time of drug consumption, tablet counts, sings and symptoms and level of consciousness in admission time in each drug types. After naloxone injection in case groups, all signs and symptoms significantly improved in all drug tyeps in comparison to control groups except nystagmus. In addition, level of consciousness significantly improved in case groups in all drug types except lorazepam. Conclusion: Findings of the study showed that naloxone is effective in management of benzodiazepines poisoning. However, future clinical trials with greater sample size are recommened.

Reference
Seger DL. ; Flumazenil-treatment or toxin. ; J Toxicol Clin Toxicol. 2004: 42(2):209-16.Seger DL. ; Flumazenil-treatment or toxin. ; J Toxicol Clin Toxicol. 2004: 42(2):209-16.

P300. BIOACTIVATION OF GLAFENINE BY HUMAN LIVER MICROSOMES AND PEROXIDASES: IDENTIFICATION OF ELECTROPHILIC IMINOQUINONE SPECIES AND GLUTATHIONE CONJUGATES

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Glafenine (Privadol; 2,3-dihydroxypropyl 2-[(7-chloro-4-quinolinyl)amino]benzoate) is a non-narcotic analgesic agent widely used for the treatment of pains of various origins. Severe liver toxicity and a high incidence of anaphylaxis were reported in patients treated with glafenine, eventually leading to its withdrawal from market in most countries. It is proposed that bioactivation of glafenine and subsequent binding of reactive metabolite(s) to critical cellular proteins play a causative role. The study described herein aimed at characterizing pathways of glafenine bioactivation and the metabolic enzymes involved. Two glutathione (GSH) conjugates of glafenine were detected in human liver microsomal incubations using liquid chromatography-tandem mass spectrometry (LC/MS/MS). The structures of detected conjugates were determined as GSH adducts of 5-hydroxyglafenine (M3) and 5-hydroxy glafenic acid (M4), respectively. GSH conjugation took place with a strong preference at C-6 of the benzene ring of glafenine, *ortho* to the carbonyl moiety. These findings are consistent with a bioactivation sequence involving initial P450-catalyzed 5-hydroxylation of the benzene ring of glafenine, followed by two electron oxidations of M3 and M4 to form corresponding *para*-quinone imine intermediates that react with glutathione to form GSH adducts M1 and M2, respectively. Formation of M1 and M2 was primarily catalyzed by heterologously expressed recombinant CYP3A4, and to a less extent, CYP2C19 and CYP2D6. We demonstrated that M3 can also be bioactivated by peroxidases, such as horseradish peroxidase and myeloperoxidase. In summary, these findings suggested that bioactivation of glafenine may result in GSH depletion, oxidative stress and covalent binding to proteins, potentially leading to hepatotoxicity.